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Chromosome Mosaicism in Patients with Normal and Abnormal Y-Chromosome

R. Schellberg[1], G. Schwanitz[1], H.-U. Schweikert[2] and R. Raff[1]

1. Institute for Human Genetics, University of Bonn, Germany
2. Medical Policlinic, University of Bonn, Germany

KEY WORDS Gonosomal mosaicism; derivative Y-chromosome; genotype-phenotype correlation.

ABSTRACT Gonosomal mosaicism with a Y-chromosome present in at least one cell system was investigated in 29 patients. In 15 cases the Y-chromosome was structurally normal, in 14 cases different structural aberrations were analysed. 17 patients were phenotypically male, 7 were female and 5 showed intersexual external genitals. The patients age at the time of chromosome investigation ranged from the prenatal period up to the age of 38 years. The most frequent clinical findings were: growth retardation, abnormalities of the external genitals, kidney malformations and different types of heart defects. Cytogenetic investigations combined metaphase and interphase analyses with FISH *(DNA probes: wcp X and Y; CEP X and Y; Yph 3.4)*. Between 2 and 5 cell systems per patient were analysed with special emphasis on their origin from different blastodermic layers. An unequal distribution of the mosaics could be demonstrated comparing the different cell systems of a proband, with no preferential combination of karyotype and cell type. The majority of tissues had two different karyotypes in probands with normal or abnormal Y-chromosome. The highest number of cell lines in one cell system was four. Patients with a ring Y-chromosome revealed the highest karyotype instability with segregation abnormalities being combined with partial amplifications of the ring. There were no age-dependent karyotype changes in our investigation group.

INTRODUCTION

Chromosomal mosaicism is defined as the presence of more than one population of cells in an individual tissue that differ in its chromosomal constitution (Furman 1999). It is difficult to estimate the frequency of gonosomal mosaicism since not all persons with a mosaic attract attention and are therefore not checked out cytogenetically. A study of Gravholt et al. (1991) defines the frequency of gonosomal mosaicism among newborns in a given cell system as 1: 1000. Conventional karyotyping of lymphocytes reveals that about 50% of patients with Turner-Syndrome (45,X) show a mosaic including additional cell lines, such as 46,XX, 46,XY, or 47,XXX (study of the American Academy of Pediatrics 1995). Due to improved diagnostics, it is assumed that survival of females with an X monosomy is only possible because of an existing second cell line (Hook and Warburton 1983).

In order to describe a patient's chromosomal mosaicism accurately, it seems necessary to analyse different somatic cell systems.

One focal point of the investigations presented here was to verify whether there exists a cell system that has a preferential karyotype distribution or not. The following investigations comprise a group of patients in whom the first somatic cell system revealed a gonosomal mosaicism. Up to 5 further cell systems per patient were analysed combining chromosome analyses with interphase FISH. Special emphasis was given to the comperative investigation of cell systems originating from different blastodermic layers.

INVESTIGATION GROUP

The investigation group (Table 1) comprises 29 cases of gonosomal mosaicism with a normal or derivative Y-chromosome (cases 1-15, normal gonosomal structure; cases 16-29, structural abnormalities) (Table 2). For each patient, between 2 and 5 different cell systems were analysed. The time of investigation ranged from the prenatal period up to the age of 38 years. The most frequent clinical findings were: growth retardation, abnormalities of the external genitals, kidney malformations and different types of heart defects (Table 1).

17 patients were phenotypically male, 7 were

Corresponding Author: Ruth Schellberg, Institut für Humangenetik, Wilhelmstrasse 31, 53111 Bonn, Germany
Phone: 00-49- (0)228/ 287 2152
Fax: 00-49- (0)228/ 287 2545
E-mail: rschellberg@yahoo.com

Table 1: Indication for chromosome analysis, age of investigation and clinical findings

	Case	Age	Phenotype
Normal Structure of Y-Chromosome	1.	16. GW	male, indication: advanced maternal age
	2.	21. GW	male, indication: advanced maternal age
	3.	1 DAY	male, indication: advanced maternal age
	4	3 Days	intersexual, pseudohermaphroditism masc., prenatal diagnosed hypotrophia, thombopenia, anemia
	5	1 Month	intersexual, hypospadia, scrotum bipartitum, tumor in the left gonad
	6	1 Month	male, hypospadia, ovotestis, stenosis of the renal pelvis on the right side
	7	1 Month	intersexual, hermaphroditism verus
	8	5 Months	male, scrotal tag, clup feet, foramen ovale, epicantic folds
	9	7 Months	male, micropenis, testis aplasia
	10	1 Year	intersexual
	11	12 Years	female, growth retardation
	12	14 Years	female, Turner-syndrome, bilateral gonado-blastoma, streak-gonads, uterus, tubae, growth retardation
	13	14 Years	female, elevated testosterone levels, growth retardation
	14	32 Years	male, Klinefelter-syndrome
	15	38 Years	male, ICSI-therapy
	16	16+1 GW	male, indication: advanced maternal age, twin pregnancy after ICSI-therapy, aortic stenosis
Structural Aberrant Y-Chromosome	17	1 Day	female, malformations of external genitalia, cardiovascular malformations
	18	2 Months	female, clitoral hypertrophia, AVSD, aortic stenosis
	19	2 Years	intersexual, hypospadia
	20	2 Years	male, hypospadia, bilateral maldescensus testis
	21	5 Years	male, hypoganadism
	22	6 Years	female, gonadal dysgenesia, growth retardation
	23	11 Years	female, Turner-syndrome, streak-gonads, hypotension, growth retardation
	24	13 Years	male, hypogonadism
	25	13 Years	male, Klinefelter syndrome
	26	15 Years	male, growth retardation
	27	24 Years	male, azoospermia, androgene-resistence, growth retardation
	28	33 Years	male, complete azoospermia
	29	36 Years	male, hypogonadism, azoospermia

female and 5 showed intersexual external genitals.

METHODS

Semi-direct preparations of chorionic villi (12 h incubation) and long-term cultures of fibroblasts, PHA-stimulated 72 h lymphocyte cultures and preparations of buccal mucosa were done according to standard cytogenetic procedures. FISH was performed following the manufactures instructions. Cell preparations and banding techniques were applied according to standard protocols. The banding methods were GTG, QFQ, RBA, CBG and DA/DAPI. Structural aberrant Y-chromosomes were further analysed by FISH (probes CEP Y, wcp Y, Y ph 3.4).

The following cell systems were analysed in metaphase: lymphocytes (n=29), amniocytes (n=4), skin biopsies (n=4), gonad biopsies (n=5), testis parenchym (n=1), placenta (n=3), umbilical cord (n=3) (Fig. 1). Interphase analyses were performed by FISH with repetitive DNA probes (CEP X, CEP Y, control CEP 18). The interphase investigations comprised the following cell types: leucocytes (n=3), buccal mucosa (n=14), cells of hair bulbs (n=4), placenta (n=7), prepuce (n=7), gonadal stalk (n=1), gonad (n=2), achilles tendon (n=1), skin (n=4), muscle (n=1) (Fig. 2).

In cases of metaphase analyses, less than 50 mitoses of the cell cultures could be investigated in 15%, about 50 mitoses in 40%, 100 and more in 45%.

Interphase diagnosis was based on a higher average of nuclei counted (maximum: 689 nuclei): less than 50 nuclei were analysed in 3%, about

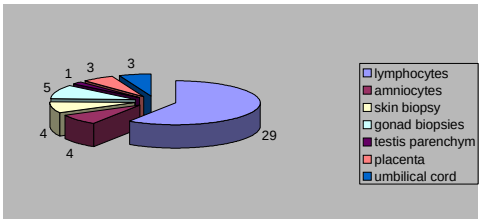

Fig. 1. Number of metaphase investigations in 7 different cell systems (n=49)

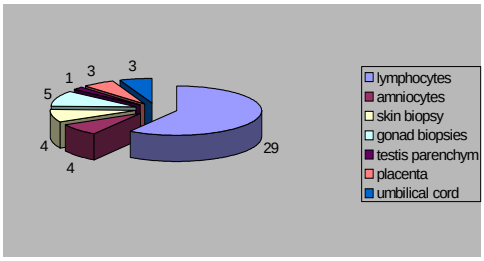

Fig. 2. Number of interphase investigations in 10 different cell systems (n=44)

50 in 18%, 100 and more in 79%. The hybridisation efficiency was more than 98% permitting an accurate analyse of the mosaic-cases (Fig. 3+4).

The statistical computation was calculated with the program "SPSS" version 9.0 for Windows.

RESULTS

In the investigation group presented here, the majority of patients (59%) was phenotypically male, females (24%) and intersexes (17%) were less frequent .

The amount of cells with the karyotype 45,X ranged from 0-100% per cell system. Classified into three groups: it was dominating (60-100%) in 19/77 tissues or 25%, it showed an almost equal frequency to the XY-karyotype (40-60%) in 10/77 or 13%, and it was less frequent (0-40%) in 48/77 or 62%. In 13 of the 17 male patients the karyotype 45,X was analysed in part of the cells. The frequency of 45,X- cells in males with regard to the three classes defined above was 71:13:16%, in 7 females it was 55:0:45%, and in intersexes it was 13:50:37%. In males the low percentage of 45,X cells(0-40%) is dominating as expected. In intersexes the middle group (40-

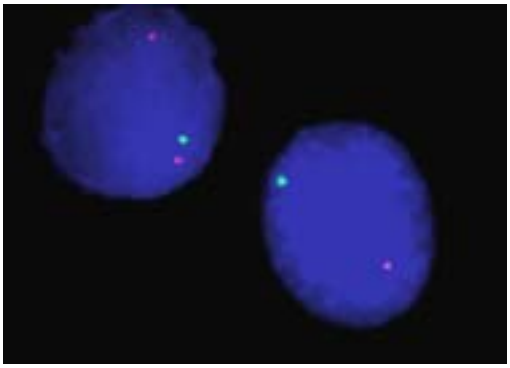

Fig. 3. FISH on nuclei of buccal mucosa; karyotype:46,XY/47,XYY (case 8); probes: CEP Y(red) and CEP X (green) (Vysis)

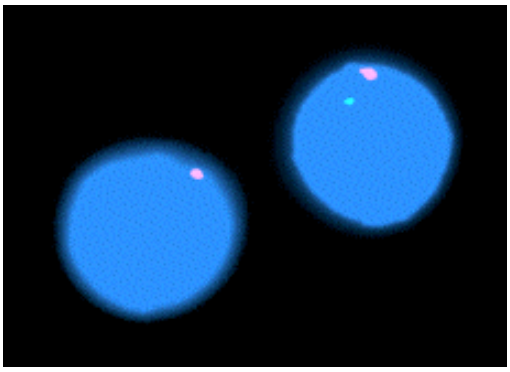

Fig. 4. FISH on nuclei of prepuce; karyotype: 45,X/46,XY (case 10); probes: CEP Y(green) and CEP X (red) (Oncor)

Fig. 5. Isodicentric Y-chromosome with inactivation of one centromere: part of a metaphase (CBG-banding)

60%) is the highest which is in accordance with an intersexual phenotype. Unexpected was the high frequency of 46,XY cells (5.5% of cells only 0-40% monosomy X) in the females. Here further investigations are required. In four patients (3

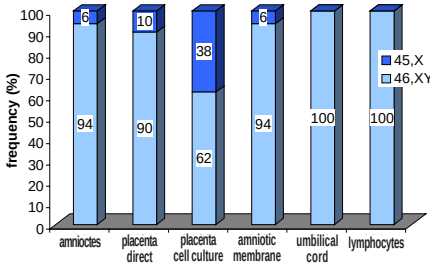

Fig. 6. Distribution of two karyotypes in four different cell systems (case 1, male patient)

males, 1 intersexual) no monosomy X-cell line was detected (cases 7-9,14), although the different karyotypes analysed make it probable that the postzygotic mitotic nondisjunction lead to such cell lines. There were no age-dependent karyotype changes in our investigation group. The types of rearrangement in patients with aberrant Y-chromosomes were idic(Y)(p and q) in 50%, del(Yq) in 21.5%, r(Y) in 21.5% and i(Yp) in 7%. The number of different karyotypes per tissue in patients with normal and aberrant Y-chromosome revealed no significant differences (Table 3).

In total 93 cell preparations were analysed. One cell line-karyotype was found in 13 cell systems, two different karyotypes in 55 cell systems, three in 19, and four in two cell systems. Comparing the different types of rearrangement of the Y-chromosome the r(Y) showed the highest instability (Table 3)

An unequal distribution of the mosaic could be demonstrated in the single patient (Fig. 6) as well as in the different cell systems. Comparing the karyotype distribution, neither the comparison of the different patients nor that of the different cell systems revealed preferential combinations. Cell systems frequently examined were lymphocytes (n=29), buccal mucosa (n=14), prepuce (n=7), skin (n=8), gonads (n=7). In all cases where gonads were examined a mosaic was found (Table 2).

In 13 cases only one single karyotype was analysed in one of the following cell systems: lymphocytes 68%, buccal mucosa 8%, prepuce 8%, skin 8%, umbilical cord 8%. The distribution of different karyotypes in cell systems investigated was calculated by χ^2- test. It could be excluded that one of the cell systems investigated had a preferential karyotype distribution.

Our findings lead to the conclusion that the analysis of lymphocyte cultures, the most frequently analysed cell system does not reveal a gonosomal mosaic in a relevant number of cases.

DISCUSSION

Mosaicism is caused by postzygotic aberrant mitoses and leads to numerical or structural aberrations or a combination of both. The karyotype of the zygote can be normal or abnormal.

If a Y-chromosome shows a structural aberration, mosaics can be found more often than in cases were the structure of the gonosomes is normal, caused by the instability of the derivative Y-chromosome in mitoses. This could not be demonstrated in our investigation group, probably caused by a too low number of patients in both groups. Types of mutation are isochromosomes (monocentric or dicentric), inverted chromosomes, partial or complete duplications, ring-chromosomes or derivative Y-chromosomes. All of them lead to problems of replication in S-phase and of distribution in the anaphase and telophase.

Table 3: Number of cell lines per tissue in patients with normal and aberrant Y-chromosome

Structure of Y-Chromosome	*Number of cell line-karyotypes and their frequency in the different types of Y-chromosome (%)*			
	1	*2*	*3*	*4*
normal	14	64	18	4
aberrant idic (Y)	14	59	27	-
del (Y)	33	67	-	-
r (Y)	9	55	36	-
i (Yp)	50	50	-	-
average value (%)	19	58	23	

The instability of the Y-chromosome can even lead to a higher number of karyotypes. These in turn can develop into different cell lines themselves (Hsu 1994).

At the end of the first gestational week the conceptus differentiates into fetal and extrafetal parts followed by the separation of the fetal tissue into different blastomeric layers and tissues. It seems very possible that the different cell lines extend unequally in different cell systems. In the past, several *in vivo* studies showed a successive increase of the normal karyotype (46,XY) and a reduction of the pathological karyotype (45,X) (Pätau 1964; Hecht 1966; Porter et al. 1969; Nielsen and Krag-Olsen 1980; Gravholt et al. 1991). In contrast, a long-time-study over a period of ten years showed an increase of the pathological karyotype (45,X) (Mc Corquodale and Boudle 1984). The authors explained this phenomenon by a shorter cell cycle of the 45,X karyotype.

In our investigation group, the lymphocytes most frequently compared to other cell systems had only one single karyotype (Table 2: cases 6,11,13,19, 24-26); the karyotype being normal as well as abnormal. This might be explained by a secondary selection *in vivo*, an occurrence that is well known from different autosomal aberrations: There, this peculiarity is analysed most frequently in cases with additional isochromosome 12p, which gets lost already in the fetal blood during early pregnancy (Schubert et al. 1997).

Obviously, any single cell system cannot provide a clear result for the complete organism containing a mosaic. The most common cell system analysed are T-lymphocytes in peripheral blood. But these analyses often do not show a correlation between the phenotype of the proband and the specific mosaicism of the single cell system. Consequently conventional analysis of lymphocytes keeps the risk of missing gonosomal mosaicism. Therefore it seems very effective to combine conventional cytogenetic analyses with interphase-FISH and to examine lymphocytes in metaphase and buccal mucosa cells in interphase: two cell systems that originate from different blastodermic layers.

The comparison of reviews of postnatally and prenatally diagnosed cases with gonosomal mosaicism shows significant differences in the phenotypic outcome of the probands, obviously due to biased ascertainment of postnatally diagnosed cases.

Our investigation group comprises four prenatally analysed male fetuses, indication for the prenatal diagnosis was the increased maternal age. Furthermore, our investigation group consists of 25 probands (0-38 years) that were diagnosed because of their abnormal phenotypes.

The two groups have to be discussed separately. 90% of the prenatally diagnosed 45,X/46,XY mosaic-cases are associated with a normal male phenotype. Some of these patients develop hypogonadism and have problems in the secondary sexual differentiation: these patients carry a high risk for gonadoblastoma, so that further investigations are indicated regularly (Raff, 2000). For all prenatal diagnosed 45,X/46,XY mosaic-cases, additional investigations are recommended to get more information on the frequency of the 45,X-cell line in different tissues and to enable a better prognosis of the phenotypic development of the probands (cases 1-4, 16 in this investigation). An estimation of phenotypic effects is difficult to predict by chromosome analysis from one cell system or before birth, as the proportion of different chromosome complements may vary from tissue to tissue. Besides, there should be regular controls in order to exclude the development of a gonadoblastoma (Petrovic et al. 1992).

All postnatally diagnosed cases of our investigation group showed abnormalities of the external genitals or infertility as an indication for chromosome analysis. Further frequent malformations were growth retardation, heart defects and kidney malformations. Additional cytogenetic investigations in further cell systems were performed depending on the clinical findings and the age of the patient. A genetic counselling was offered in each case.

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Table 2: Cytogenetic findings in patients with gonosomal mosaicism

Case	*Examined cell systems*	*Karyotype with relative frequency of cell lines*		*Cell stage*
		First investigation	*Following investigations*	
1	amniocytes	45,X/46,XY 6: 94		metaphase n=100
	placenta direct		45,X/46,XY 10: 90	interphase n=50
	cell culture		45,X/46,XY 38: 62	metaphase n=51
	amniotic membrane		45,X/46,XY 6: 94	metaphase n=52
	umbilical cord		46,XY 100%	metaphase n=53
	lymphocytes		46,XY 100%	metaphase n=32
2	amniocytes	45,X/46,XY 15: 85		metaphase n=50
	placenta		45,X/46,XY 32: 68	interphase n=100
	umbilical cord		45,X/46,XY 15: 85	metaphase n=50
	lymphocytes		45,X/46,XY 2: 98	metaphase n=50
3	amniocytes	45,X/46,XY 40: 60		metaphase n=44
	placenta 2 different areas		45,X 100	metaphase n=49
			45,X/46,XY 29: 71	metaphase n=28
	amniotic membrane		45,X/46,XY 83: 17	metaphase n=60
	umbilical cord		45,X/46,XY 61: 39	metaphase n=57
	lymphocytes		45,X/46,XY 54: 46	metaphase n=54
4	lymphocytes	45,X/46,XX/46,XY/47,XXX relation not exact defined		metaphase n=?
	prepuce		45,X/46,XX/46,XY/47,XXX 17: 62: 14: 7	interphase n=100
5	lymphocytes	45,X/46,XY 56: 44		metaphase n=53
	gonadal stalk		45,X/46,XY 51: 49	interphase n=51
	gonad (left)		45,X/46,XY 50: 50	interphase n=50
	muscle biopsy		45,X/46,XY 46: 54	interphase n=13
	skin biopsy		45,X/46,XY 75: 25	interphase n=53
6	lymphocytes	45,X 100		metaphase n=50
	buccal mucosa		45,X/46,XY/47,XXY 84: 15: 1	interphase n=122
7	lymphocytes	46,XX/47,XXY 90: 10		metaphase n=50
	prepuce		46,XX/46,XY/47,XXY 91: 7: 2	interphase n=100
8	lymphocytes	46,XY/47,XYY 10: 90		metaphase n=50
	buccal mucosa		46,XY/47,XYY 70: 30:	interphase n=58
9	lymphocytes	46,XY/47,XYY relation no exact defined		metaphase n=?
	prepuce		47,XYY 100	interphase n=100

Case	*Examined cell systems*	*Karyotype with relative frequency of cell lines*		*Cell stage*
		First investigation	*Following investigations*	
10	lymphocytes	45,X/46,XY relation not exact defined		metaphase n=?
	prepuce		45,X/46,XY 4: 96	interphase n=100
11	lymphocytes	46,XY 100		metaphase n=77
	buccal mucosa		45,X/46,XY 40: 60	interphase n=100
12	lymphocytes	45,X/46,XY 12: 88		metaphase n=53
	right gonad		45,X/46,XY 38: 62 45,X/46,XY 26: 74	metaphase n=50 interphase n=100
	left gonad		45,X/46,XY 30: 70	metaphase n=50
13	lymphocytes	45,X 100		metaphase n=50
	buccal mucosa		45,X/46,XY 96: 4	interphase n=111
	skin biopsy		45,X/46,XY 93: 7	interphase n=100
14	lymphocytes	47,XXY/48,XXXY 96: 4		metaphase n=50
			46,XX/46,XY/47,XXY 2: 5: 93	metaphase n=50
	leucocytes		46,XX/46,XY/47,XXY 5: 5: 90	interphase n=100
	buccal mucosa		46,XX/46, XY/47,XXY 5: 5: 88	interphase n=60
15	lymphocytes	45,X/46,XY/47,XXY 8: 90: 2		metaphase n=98
	buccal mucosa		45,X/46,XY/47,XXY 15: 82: 3	interphase n=417
	cells of hair bulb		45,X/46,XY/47,XXY 16: 78: 6	interphase n=228
	skin biopsy		45,XY/47,XXY 87: 13	interphase n=52
16	amniocytes	45,X/46,X,idic(Yq) 36: 64		metaphase n=136
	lymphocytes		45,X/46,X,idic(Yq) 47: 53	interphase n=100
17	lymphocytes	45,X/46,X,idic(Yq)/47,X,2idic(Yq) 33: 54: 13:		metaphase n=100
	skin biopsy		45,X/46,X,idic(Yq) 28: 72	interphase n=100
	achilles tendon		45,X/46,X,idic(Yq) 31: 69	inerphase n=100
18	lymphocytes	45,X/46,X,idic(Yq)/47,X,2idic(Yq) 3: 54: 13		metaphase n=50
	buccal mucosa		45,X/46,X,idic(Yp)/47,X,2idic(Yp) same mosaic	n=50 <20 cells
19	lymphocytes	46,X,del(Yq) 100		metaphase n=30
	prepuce		45,X/46,X del(Yq) 77: 23	interphase n=100
20	lymphocytes	45,X/46,X,idic(Yq) 14: 86		metaphase n=50
	leucocytes		45,X/46,X,idic(Yq) 8: 92	interphase n=100
	prepuce		45,X/46,X,idic(Yq) 93: 7	interphase n=100
	buccal mucosa		45,X 100	interphase n=100

Case	*Examined cell systems*	*Karyotype with relative frequency of cell lines*		*Cell stage*
		First investigation	*Following investigations*	
21	lymphocytes	46,X,idic(Yp)/47,X,2idic(Yp) 95: 5		metaphase n=92
	buccal mucosa		46,X,idic(Yp)/47,X,2idic(Yp) 94: 6	interphase n=351
	cells of hair bulb		46,X,idic(Yp)/47,X,2idic(Yp) 95: 5	interphase n=207
	skin biopsy		46,X,idic(Yp) 100	metaphase n=30
22	lymphocytes	46,X/46,X,r(Y) 39: 61		metaphase n=128
	ovary (right)		45,X/46,X,r(Y) 70: 30	interphase n=100
	ovary (left)		45,X/46,X,r(Y) 95: 15	interphase n=100
	buccal mucosa		45,X/46,X,r(Y) 87: 13	interphase n=98
	cells of hair bulb		45,X/46,X,r(Y) 76: 24	interphase n=170
23	lymphocytes	45,X/46,X,idic(Yp) 62: 38		metaphase n=50
	gonad (right)		45,X/46,X,idic(Yp) 75: 25	metaphase n=36
	gonad (left)		45,X/46,X,idic(Yp) 97: 3	metaphase n=33
24	lymphocytes	46,X,idic(Yp) 100		metaphase n=50
	parenchyma testis		45,X/46,X,idic(Yq)/47,X,2 idic(Yq) 12: 74: 14	metaphase n=100
	buccal mucosa		46,X/46,X,idic(Yq)/47,X,2 idic (Yq) 16: 65: 19	interphase n=100
	skin biopsy		45,X/46,X,idic(Yq)/47,X,2 idic (Yq) 3: 87: 10	metaphase n=100
25	lymphocytes	46,X,i(Yp) 100		metaphase n=39
	leucocytes		46,X,i(Yp) 100	interphase n=50
	testis (right)		45,X/46,X,i(Yp)/47,X,2 i(Yp) 12: 74: 14	metaphase n=50
	skin biopsy		45,X/46,X,i(Yp)/47,X,2 i(Yp) 3: 87: 10	metaphase n=80
26	lymphocytes	46,X,r(Y) 100		metaphase n=29
	buccal mucosa		45,X/46,X,r(Y)/46,X,dup r(Y) 43: 56: 1	interphase n=689
	cells of hair bulb		45,X/46,X,r(Y)/46,X,dup r(Y) 42: 50: 8	interphase n=50
	skin biopsy		45,X/46,X,r(Y) 60: 40:	interphase n=205
27	lymphocytes	46,X,del(Y)(q11.2) 100		metaphase n=30
	prepuce		45,X/46,X,del(Y)(q11.2) 2: 98	interphase n=100
28	lymphocytes	45,X/46,X,r(Y)/46,X,dup r(Y) 48: 45: 7		metaphase n=182
	buccal mucosa		45,X/46,X,r(Y)/46,X,dup r(Y) 25: 36: 39	interphase n=100
29	lymphocytes	46,X/46,X,del(Y) 6: 94		metaphase n=100
	buccal mucosa		45,X/46,X del(Y) 77: 23	interphase n=60

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